date. A marked up copy of the amended and canceled claims, showing the changes made using underlining and bracketing, is attached to this response.

REJECTIONS

Priority

Applicants respectfully note that the Examiner has acknowledged Applicant's claim for foreign priority "based on an application filed in Great Britain on May 21, 1998," however the instant application claims priority to a Great Britain application (i.e. GB 9711040.7) that was filed on May 29, 1997. Accordingly, Applicants request acknowledgement of this earlier claim to foreign priority and/or clarification on this point.

Double Patenting

Claims 1-6 and 8-57 have been rejected under the judicially created doctrine of obviousness-type double patents as being unpatentable over claims 1-6 and 8-57 of U.S. Patent No. 6,268,142. Applicants respectfully request that this double patenting rejection be held in abeyance until a finding of allowable subject matter is made, at which time Applicants will file a terminal disclaimer if necessary.

Claim 7 has been rejected under 35 U.S.C. 101 for statutory double patenting as claiming the same invention as that of claim 7 of prior U.S. Patent No. 6, 268, 142. Applicants have canceled claim 7, thereby obviating this rejection.

Rejections under 35 U.S.C. § 112, first paragraph- written description

Claims 1-6 and 8-57 have been canceled under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the applicant, at the time the application was filed, had possession of the claimed invention. In particular, the Office Action cites *University of California v. Eli Lilly and Co.* in support of the rejection of these claims. Applicants respectfully traverse this rejection in view of the claims as amended.

In particular, Applicants note that they have amended subject claims 1-6, 8-20 and 29-40 so as to be limited to particular IL-1 inflammatory haplotypes which are supported extensively in the application as filed. Furthermore, Applicants note that the holding in *Eli Lilly* applied to nucleic acid/gene-type composition claims, while the instant application is directed to methods of use claims where the element of novelty does not draw exclusively from the uniqueness of the nucleic acid sequences concerned. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103- obviousness

The Examiner has made a number of rejections under 35 U.S.C. § 103(a) by combining various references and asserting that the combined teachings render the claimed invention *prima facie* obvious to one of ordinary skill in the art at the time of the invention. Applicants have traversed these obviousness rejections individually below. In each instance, the Examiner has failed to show that the claimed invention is *prima facie* obvious in light of the combination of teachings from the cited references. In several instances, Applicants have pointed out that the cited reference fails to provide the teachings asserted by the Examiner. Applicants respectfully request reconsideration of the rejected claims in light of these traversals and, still further, in light of amendments made to claims which are included with this response.

Prior to reconsideration of the rejected claims, Applicants respectfully request that the Examiner carefully reconsider the rejected claims in light of the amendments made with this action. In particular, the amendments limit the subject claims to the specific IL-1 inflammatory haplotypes which have been described and characterized in the instant application. Applicants further respectfully note that the invention provides multiple advantages over other methods of diagnosing and treating inflammatory diseases. For example, the instant invention provides improvements over available prior art methods inasmuch as it provides for diagnostic and treatment methods based upon Il-1 inflammatory haplotype information, comprising certain allelic patterns of a plurality of alleles of an IL-1 inflammatory haplotype, thereby providing increased reliability in predicting and treating inflammatory disease. In contrast, the references cited by the

Examiner fail to teach or suggest such allelic patterns or the IL-1 inflammatory haplotypes of the instant invention. The deficiencies of each of five different combinations of seven different prior references asserted by the Examiner under 35 U.S.C. §103(a) are considered individually below.

(1) Wang et al., in view of Duff et al. or Bioque et al.

Claims 1-4, 8-10, 13-31 and 34-40 have been rejected under 35 U.S.C. §103 (a) over Wang et al. (U.S. Patent No. 5,681,940) in view of Duff et al. (U.S. Patent No. 5,698,399), or, in the alternative, in view of Bioque et al. (Clinical and Experimental Immunology (1995) 102: 379-83). Applicants respectfully traverse this rejection because the cited references do not render the claimed invention, as reflected in the claims as amended with this action, obvious either alone or taken in combination. In particular the Wang et al. reference is relied upon for a number of teachings which, in fact, it does not provide as described in detail below. Furthermore, even if Wang et al. did provide the teachings for which the Examiner has relied upon it, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Applicants respectfully submit that Wang et al., in view of Duff et al., or Bioque et al. fail to provide any motivation to combine the cited references that would be within the skill in the art at the time the application was filed.

Contrary to the assertions of the Examiner, Wang et al. fails to teach the detection of polymorphisms in general, or of IL-1 polymorphisms or allelic patterns of an IL-1 inflammatory haplotype in particular, as claimed in the instant application (see amended claims 1, 8, 21, and 29). Rather, Wang et al. teaches "Sugar Modified Nucleosides and Oligonucleotides" utilizing phosphoamidite chemistry to render potential antisense therapeutics more resistant to nucleases and more readily taken up by host cells. Indeed Wang et al., mentions the IL-1 gene only in passing as one of many potential targets for

antisense inhibition (see column 7, lines 22-29). Wang et al. does not teach the detection of DNA polymorphisms in general or IL-1 polymorphic alleles in particular. Indeed, the Wang et al. reference does not appear to even mention the existence of DNA polymorphisms. Accordingly, the Examiner has not provided a cogent basis for citing the Wang et al reference against claims 1-4, 8-10, 13-20, 29-31, or 34-40. Furthermore, while Wang et al. states that the subject oligonucleotides "may also be advantageously substituted for conventional oligonucleotides in many non-therapeutic techniques such as hybridization to detect nucleic acid sequences, the polymerase chain reaction, and the like" (column 8, lines 1-5), it fails to render claims 21-28 obvious in combination with the cited secondary references for the reasons which follow in Applicants' discussion of the shortcomings of the Duff et al. and Bioque et al. references, and because a skilled artisan would not have been motivated to combine the teachings related to IL-1 polymorphic alleles from either Duff et al. or Bioque et al. with the teachings related to antisense oligonucleotides supplied by Wang. In the interest of preserving the record, Applicants have provided below a specific and detailed enumeration of the shortcomings of the Wang et al. reference.

First, the Examiner states that "Wang et al. teaches a method for determining whether a subject has or is predisposed to developing a disease or condition that is associated with IL-1 comprising detecting at least one gene wherein the presence of the gene indicates that the subject is predisposed to the development or has the disease or condition (column 7, lines 2-34)." The cited reference teaches "therapeutic applications" of the sugar modified oligonucleotides of the invention such as "to mediate antisense inhibition of numerous genetic targets...(including)... cytokines (IL-1, IL-2, IL-3, IL-4, IL-6 and the like)". Thus, the cited reference teaches the use of antisense oligonulceotides to inhibit any of a number of possible gene targets. Notably, this reference does not teach or suggest the detection of a polymorphic variant of the IL-1 gene locus, as required in claims 1-4, 8-10, 13-20, 29-31 and 34-40. Still further, the reference does not teach or suggest the method of claims 21-28, which are drawn to methods of determining the effectiveness of treating an IL-1 polymorphism-associated disease with a particular dose of a particular therapeutic by detecting the level of IL-1 protein or nucleic acid in a sample obtained from a subject before administration of the

therapeutic, as compared to the level of IL-1 protein or nucleic acid in a sample obtained from the subject after administration of the therapeutic.

Second, these deficiencies are not made up for by other teachings provided by the Wang reference and cited by the Examiner. For example, the Examiner points out that "Wang et al. teaches a method wherein the disease of (sic) condition is selected from the group consisting of inflammatory disease, a degenerative disease, an immunological disorder, an infectious disease, a trauma induced disease, and a cancer (Column 7, lines 30-67)." The cited excerpt mentions that the antisense derivatized oligonucleotides of the condition can be used to "mediate antisense inhibition of numerous genetic targets" (column 7, line 21) including "target genes or RNAs...associated with...inflammatory conditions" (column 7, lines 30-32) and "both in vivo and ex vivo therapeutic applications" (column 7, line 36)...(such as)..."modulation of inflammatory responses by modulating expression of genes such as...IL-1" (column 7, lines 54-56). Accordingly, these additional teachings of Wang also fail to teach or suggest the detection of an allelic pattern of an IL-1 inflammatory haplotype for the purpose of predicting disease (claims 1-4) or selecting an appropriate therapeutic to treat such disease (claims 8-10 & 13-20, and 29-31 & 34-40). Furthermore, these additional teachings of Wang also fail to teach or suggest a method of determining the effectiveness of a particular IL-1 polymorphism-associated disease therapeutic by monitoring the level of an IL-1 protein or nucleic acid (claims 21-28).

Third, the foregoing deficiencies of Wang et al. are not supplemented by the remainder of the Wang et al. reference. The Examiner states that "Wang et al. teaches a method wherein the detecting step is selected from the group consisting of hybridization and polymerase chain reaction and the like (Column 8, lines 1-9)." Applicants note that Wang et al. fails to teach or suggest the detection of an IL-1 polymorphism or the monitoring of an IL-1 protein or nucleic acid for the purpose of determining the effectiveness of a particular IL-1 polymorphism-associated disease therapeutic (claims 21-28).

Fourth, the Examiner further cites Wang et al. for teaching "a method for determining the effectiveness of treating a subject that has or is predisposed to developing a disease or condition that is associated with an IL-1 polymorphism by detecting the level, amount or activity of mRNA in a sample obtained from the subject, administering the particular therapeutic to the subject, detecting the level or mRNA and comparing the relative levels (Column 7, lines 14-34)." It is not clear how the cited section of Wang et al. teaches (or suggests) the method of claims 21-28, as paraphrased by the Examiner. In particular, the teachings of this section of Wang et al. have already been considered above and are limited to antisense oligonucleotide "therapeutic applications" of the sugar modified oligonucleotides of the invention such as "to mediate antisense inhibition of numerous genetic targets...(including)...cytokines (IL-1, IL-2, IL-3, IL-4, IL-6 and the like)". Accordingly, the asserted teachings of Wang et al. are not supported by the record and so, once again, the Wang et al. reference fails to teach or suggest the claimed invention.

Fifth, the Examiner still further cites Wang et al. for teaching "a method for selecting an appropriate therapeutic for treating...an individual that has or (is) predisposed to developing a disease or disorder that is associated with an IL-1 polymorphism, comprising the steps of: detecting whether the subject contains the polymorphism and selecting a therapeutic that compensates for a causative mutation that is in linkage disequilibrium with the IL-1 polymorphism (Column 8 (7?), lines 14-34 and Column 8, lines 1-9)." The cited sections of Wang do not provide such guidance. In particular, the cited sections do not teach the detection of a polymorphic allele of any gene in general or IL-1 in particular, and, further, do not teach the selection of therapeutics in accord with such a polymorphic allele. Accordingly, the Wang et al. reference again fails to provide the guidance asserted by the Examiner and, therefore, does not teach or suggest the claimed invention.

Sixth, and finally, the Examiner cites Wang et al. for teaching "a method wherein the modulator (of) activity is an agonist or antagonist nucleic acid (column 7, lines 20-34)." As discussed above, this section of Wang et al. discusses the application of the modified oligonucleotides of the invention for the purpose of antisense inhibition of any

gene, including cytokine-encoding genes such as IL-1. Accordingly, it is not clear how Wang et al. could be construed to teach anything more than antagonist nucleic acids (antisense), and, as discussed in connection with Duff et al. and Bioque et al., this guidance fails to render the claimed invention obvious to one of skill in the art.

Next, the Office Action states that the Wang et al. reference "does not teach the association of disease (or) condition with at least one allele of (an) IL-1 inflammatory haplotype," but that the Duff et al. reference (Abstract) and the Bioque et al. reference (Summary) "teaches the association of (a) disease (or) condition with at least one allele of (an) IL-1 inflammatory haplotype (Abstract)." The Office Action goes on to state that it "would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the IL-1 inflammatory haplotype associated disease detection model of Duff et al. in the method of Wang et al. since Wang et al. states, 'Oligonucleotides of the present invention are suitable for use in both in vivo and ex vivo therapeutic applications (Column 7, lines 35-36).'" The Office Action further states that "an ordinary practitioner would have been motivated to combine the Il-1 inflammatory haplotype associated disease detection model of Duff et al. or Bioque et al. in the method of Wang et al. in order to achieve the express advantages noted by Wang et al. of a system which can provide oligonucleotides suitable for use in both in vivo and ex vivo therapeutic applications." Applicants respectfully disagree for the reasons which follow.

First, the Duff et al. patent fails to render the instant claimed invention obvious under 35 U.S.C. § 103 in combination with the Wang et al. reference. The Wang et al. reference fails to provide the cited teachings for the reasons described above. Nevertheless, even assuming the Wang et al. reference did in fact provide such teachings, and still further assuming that the Duff et al. reference is properly asserted under 35 U.S.C. § 103 (see below), Duff et al. fails to provide the asserted teachings necessary to supplement the supposed limitations of the Wang et al. reference. In particular, Duff et al. fails to teach an IL-1 haplotype or the allelic patterns of the IL-1 haplotypes taught in the instant application. Indeed, the Duff reference teaches the detection and typing of only a single IL-1 polymorphism (that of allele 2 of the IL-1RN polymorphic allele). In

contrast, the instant application teaches many polymorphic alleles of the IL-1 locus which together constitute certain "inflammatory haplotypes." The invention teaches that by detecting an allelic pattern of more than one allele of an inflammatory haplotype, that predisposition to a number of inflammatory diseases and conditions can be predicted. In contrast, Duff et al. teaches the detection of only a single allele of a single polymorphic locus - i.e. allele 2 of the IL-1RN VNTR locus. Additional alleles of the IL-1 locus in general, or those comprising the particular inflammatory haplotypes of the invention in particular, are not taught by the Duff et al. reference and, accordingly, Duff et al. does not render the claimed invention obvious because these additional alleles of the IL-1 locus would not be obvious to the skilled artisan absent undue experimentation. Furthermore, the Duff et al. reference fails to teach or suggest the inflammatory diseases and conditions that are associated with an IL-1 inflammatory haplotype as taught in the instant application. Still further, Duff et al. teaches neither methods for determining the effectiveness of therapeutics by measuring IL-1 gene expression before and after administration of a particular dose of a particular therapeutic (claims 21-28), nor does it teach antisense therapeutics in particular. Accordingly, there would be no motivation for the skilled artisan to combine even the single polymorphism taught by Duff et al. with the antisense oligonucleotides of Wang et al. to arrive at a method even analogous to the instant claims. Therefore, the Duff et al. reference, in combination with the Wang et al. reference, fails to render the instant claimed invention obvious under either 35 U.S.C. § 103/102(a) or 35 U.S.C. § 103/102(e).

Moreover, Applicants note that, upon perfection of Applicants' claim of the benefit of foreign priority to Great Britain Application No. 9711040.7, filed May 29, 1997, the October 28, 1997 date cited by the Examiner for the Wang et al. patent is removed as prior art. Applicants note that the date cited by the Examiner (October 28, 1997) for the Wang et al. reference is the date of grant of that patent and hence its 102(a) or "publication" date. Applicants respectfully note that the Examiner has not explicitly cited the Wang patent as prior art under 35 U.S.C. § 103(a)/ 102(e). Notwithstanding the fact that the Duff et al. patent is available as prior art under 35 U.S.C. §102(e), Applicants note that the American Inventors Protection Act of 1999 (officially cited as Pub. L. No. 106-113) provides for amendment of 35 U.S.C. § 103(c) to preclude

application of subject matter which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. Applicants note that, at the time the instant invention was made, the subject matter described in the Duff et al. patent and the instant claimed invention were "owned by the same person or subject to an obligation of assignment to the same person." Applicants note that this new provision of 35 U.S.C. § 103(c) applies only to those patent applications filed on or after November 29, 1999. Accordingly, a procedural technicality precludes the application of the substantive law provided by the new provisions of 35 U.S.C. § 103(c), which would otherwise remove this reference as prior art against the instant claimed invention in an obviousness rejection. Applicants respectfully reserve the right to remove the Duff et al. reference under 35 U.S.C. § 103(c) by filing a continuing application in this case. Nevertheless, as discussed above, Applicants believe this procedural mechanism is not needed because the Duff et al reference in view of the Wang et al. reference does not render the claimed invention obvious.

The Office Action further states that, in the alternative with the Duff et al. reference, it would have been *prima facie* obvious to combine the teachings of Bioque et al. ((1995) Clinical and Experimental Immunology 102: 379-83; hereinafter Bioque et al. or the Bioque reference) with the teachings of the Wang et al. reference to arrive at the claimed invention. Applicants respectfully disagree. Bioque et al. suggests the association of particular alleles of the Il-1β and IL-1Ra genes with inflammatory bowel disease. In particular, the Bioque et al. study found that "non-carriers of IL-1β allele 2 were more often present in the subgroup of patients carrying the IL-1Ra allele 2" (see Summary) while no such association of these alleles was detected in the group of healthy controls. These observations would not lead the skilled artisan to the claimed invention which encompasses the multiple IL-1 inflammatory haplotypes described in the instant application. In particular, the Bioque et al. reference does not teach the multiple IL-1 locus spanning polymorphic alleles comprising the inflammatory haplotypes of the present invention. The detection of several such polymorphic alleles in linkage

disequilibrium provides strong predictive value to the method of the present invention. Indeed, Bioque et al. concludes that "the Il-1β gene itself is not a marker of genetic susceptibility to ulcerative colitis and Crohn's disease in the Dutch population" and further that "additional studies of this polymorphism in association with other genetic markers and functional studies will be necessary to assess the full significance of this gene in the regulation of intestinal inflammation." Thus the Bioque reference does not provide the skilled artisan with the instant invention but rather suggests the need for further research to arrive at a useful invention such as that provided in the instant application. Accordingly, and in combination with the aforementioned deficiencies in the Wang et al. reference, the Bioque et al. reference fails to render the claimed invention obvious under 35 U.S.C. § 103/102(a) and reconsideration and withdrawal of this rejection in view of the claims as amended with this action is respectfully requested.

(2) Potter et al. in view of Bioque et al.

The Office Action states that claims 41, 42, and 44-56 are rejected under 35 U.S.C. § 103(a) over Potter et al. (U.S. Patent No. 5,780, 587 (July 14, 1998)) in view of Bioque et al.. Applicants note that subject claims 41-57 have been canceled with this action and, accordingly, this rejection is rendered moot.

(3) Wang et al. in view of Bioque et al. and Weber et al.

The Office Action states that claims 1-4, 5, 8-11, 13-32 and 34-40 have been rejected under 35 U.S.C. § 103 (a) over Wang et al. (U.S. Patent No. 5,681.940) (July 14, 1998) in view of the Bioque et al. reference and further in view of Weber et al. (U.S. Patent No. 5,582,979) (December 10, 1996). Applicants respectfully traverse the assertion of the Examiner that the claims as amended with this action are rendered obvious by the combined teachings of the cited references. No *prima facie* showing of obviousness has been made for the reasons that follow.

First, Wang et al. in view of Bioque et al. fails to teach the method of claims 1-4, 8-10, 13-31 and 34-40 for the reasons described above. Second the Weber et al. reference does not supplement the deficiencies in the combined teachings of Wang et al.

and Bioque et al. Weber et al. teaches the use of primers to detect (dC-dA)n.(dG-dT)n tandem nucleotide repeat polymorphisms which "can be used to map genes which are involved in genetic diseases." The Weber et al. reference adds nothing to the deficiencies in teaching an IL-1 inflammatory haplotype which have been cited for the Wang and Bioque references. Indeed, Applicant's seek clarification from the Examiner on precisely why "SEQ ID NO. 247 of Weber et al. ... (would be combined with)... the method of Wang et al. in view of Bioque et al. in order to achieve the express advantages noted by Weber et al. of a system which can be used to map genes which are involved in genetic diseases or in other economically important traits" and, if such a combination were rendered obvious by the cited combination of references, why it would be relevant to the patentability of the claims in question which are not directed to a system of mapping genes. In this regard, the Examiner is respectfully reminded of the guidelines for examination specified in 37 C.F.R. 1.104 (c) (2), which promote the efficient prosecution of patent applications in the interest of both Applicant and the Examiner. Accordingly, reconsideration and withdrawal of the rejection in view of the claims as amended with this action is respectfully requested.

(4) Potter et al. in view of Bioque et al. and Wang et al.

The Office Action still further states that claims 41-56 have been rejected under 35 U.S.C. § 103 (a) over Potter et al. (U.S. Patent No. 5,780,587) in view of Bioque et al. and further in view of Wang et al. (U.S. Patent No. 5,681,940) (October 28, 1997). Applicants note that subject claims 41-57 have been canceled with this action and, accordingly, this rejection is rendered moot.

(5) Potter et al. in view of Bioque et al. and Yoneda et al.

Finally, the Office Action still further states that claims 41, 42 and 44-57 have been rejected under 35 U.S.C. § 103 (a) over Potter et al. (U.S. Patent No. 5,780,587) in view of Bioque et al. and further in view of Yoneda et al. (U.S. Patent No. 5,993,817) (Nov. 30, 1999). Applicants note that subject claims 41-57 have been canceled with this action and, accordingly, this rejection is rendered moot.

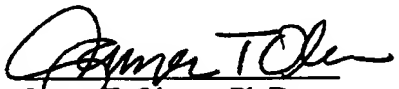
CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims now pending are in condition for allowance, and early notification of such is respectfully requested. If for any reason a telephonic conference with the Applicant would be helpful in expediting prosecution of the instant application, the Examiner is invited to call Applicants' Attorney at (617) 832-1000.

No fees are believed to be due in connection with this filing. However, if any fees are necessary with this filing, please charge the fees to our **Deposit Account No. 06-1448.**

Respectfully submitted,
FOLEY HOAG LLP

Dated: September 30, 2002



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Marked up version of claims in 09/845,129 showing changes made:

1. **(Amended)** A method for [determining] detecting whether a subject has or is predisposed to developing a disease or condition that is associated with an IL-1 inflammatory haplotype, comprising detecting [at least one allele of the haplotype] a plurality of alleles from an IL-1 inflammatory haplotype selected from the group consisting of: an IL-1 44112332 inflammatory haplotype, and an IL-1 33441461 inflammatory haplotype, wherein the presence of the plurality of alleles [allele] indicates that the subject is predisposed to the development or has the disease or condition.

2. A method of claim 1, wherein the disease of condition is selected from the group consisting of an inflammatory disease, a degenerative disease an immunological disorder, an infectious disease, a trauma induced disease, and a cancer.

3. A method of claim 1, wherein said detecting step is selected from the group consisting of:

a) allele specific oligonucleotide hybridization;
b) size analysis;
c) sequencing;
d) hybridization;
e) 5' nuclease digestion;
f) single-stranded conformation polymorphism;
g) allele specific hybridization;
h) primer specific extension; and
j) oligonucleotide ligation assay.

4. A method of claim 1, wherein prior to or in conjunction with detection, the nucleic acid sample is subject to an amplification step.

5. A method of claim 4, wherein said amplification step employs a primer selected from the group consisting of any of SEQ ID Nos.8-32.

6. A method of claim 3, wherein said size analysis is preceded by a restriction enzyme digestion.

7. **(Canceled)** A kit comprising a primer selected from the group consisting of any of SEQ ID NOs. 8-32.

8. **(Amended)** A method for selecting an appropriate therapeutic for an individual that has or is predisposed to developing a disease or disorder that is associated

with an IL-1 polymorphism, comprising the steps of: detecting a plurality of alleles from an IL-1 inflammatory haplotype selected from the group consisting of: an IL-1 44112332 inflammatory haplotype, and an IL-1 33441461 inflammatory haplotype, [whether the subject contains the polymorphism] and selecting a therapeutic that compensates for a causative functional mutation that is in linkage disequilibrium with the IL-1 [polymorphism] alleles.

9. A method of claim 8, wherein said detecting is performed using a technique selected from the group consisting of:

a) allele specific oligonucleotide hybridization;
b) size analysis;
c) sequencing;
d) hybridization;
e) 5' nuclease digestion;
f) single-stranded conformation polymorphism;
g) allele specific hybridization;
h) primer specific extension; and
j) oligonucleotide ligation assay.

10. A method of claim 8, wherein prior to or in conjunction with detecting, the nucleic acid sample is subjected to an amplification step.

11. A method of claim 10, wherein said amplification step employs a primer selected from the group consisting of SEQ ID Nos. 8-32.

12. A method of claim 9, wherein said size analysis is preceded by a restriction enzyme digestion.

13. A method of claim 9, wherein the disease or condition is selected from the group consisting of:

14. A method of claim 9, wherein the therapeutic is a modulator of an IL-1 activity.

15. A method of claim 14, wherein the IL-1 activity is IL-1α.

16. A method of claim 14, wherein the IL-1 activity is IL-1β.

17. A method of claim 14, wherein the IL-1 activity is IL-1RN.

18. A method of claim 14, wherein the modulator of an IL-1 activity is a protein, peptide, peptidomimetic, small molecule, nucleic acid or a nutraceutical.

19. A method of claim 14, wherein the modulator is an agonist.

20. A method of claim 14, wherein the modulator is an antagonist.

21. **(Canceled)** A method for determining the effectiveness of treating a subject that has or is predisposed to developing a disease or condition that is associated with an IL-1 polymorphism with a particular dose of a particular therapeutic, comprising the steps of:

a) detecting the level, amount or activity of an IL-1 protein; or an IL-1 mRNA or DNA in a sample obtained from a subject;

b) administering the particular dose of the particular therapeutic to the subject; detecting the level, amount or activity of an IL-1 protein; or an IL-1 mRNA or DNA in a sample obtained from a subject; and

c) comparing the relative level, amount or activity obtained in step a) with the level, amount or activity obtained in step b).

22. **(Canceled)** A method of claim 21, wherein the therapeutic is a modulator of an IL-1 activity.

23. **(Canceled)** A method of claim 22, wherein the IL-1 activity is IL-1α.

24. **(Canceled)** A method of claim 22, wherein the IL-1 activity is IL-1β.

25. **(Canceled)** A method of claim 22, wherein the IL-1 activity is IL-1RN

26. **(Canceled)** A method of claim 21, wherein the therapeutic is a protein, peptide, peptidomimetic, small molecule or a nucleic acid.

27. **(Canceled)** A method of claim 22, wherein the modulator is an agonist.

28. **(Canceled)** A method of claim 22, wherein the modulator is an antagonist.

29. **(Amended)** A method for treating or preventing the development of a disease or condition that is associated with an IL-1 polymorphism in a subject comprising the

steps of; detecting a plurality of alleles from an IL-1 inflammatory haplotype selected from the group consisting of: an IL-1 44112332 inflammatory haplotype, and an IL-1 33441461 inflammatory haplotype; [the presence of at least one IL-1 polymorphism comprising and IL-1 inflammatory haplotype] and administering to the subject a therapeutic that compensates for a causative mutation that is in linkage disequilibrium with the [at least one IL-1 polymorphism] IL-1 inflammatory haplotype.

30. A method of claim 29, wherein the detecting step is selected from the group consisting of:

a) allele specific oligonucleotide hybridization;
b) size analysis;
c) sequencing;
d) hybridization;
e) 5' nuclease digestion;
f) single-stranded conformation polymorphism;
g) allele specific hybridization;
h) primer specific extension; and
j) oligonucleotide ligation assay.

31. A method of claim 29, wherein prior to or in conjunction with detecting, the nucleic acid sample is subjected to an amplification step.

32. A method of claim 29, wherein said amplification step employs a primer selected from the group consisting of any of SEQ ID Nos. 8-32.

33. A method of claim 30, wherein said size analysis is preceded by a restriction enzyme digestion.

34. A method of claim 30, wherein the therapeutic is selected from the group consisting of: a modulator of an IL-1 activity.

35. A method of claim 34, wherein the IL-1 activity is IL-1α.

36. A method of claim 34, wherein the IL-1 activity is IL-1β.

37. A method of claim 34, wherein the IL-1 activity is IL-1Ra.

38. A method of claim 34, wherein the therapeutic is a protein, peptide, peptidomimetic, small molecule or a nucleic acid.

39. A method of claim 34, wherein the modulator is an agonist.

40. A method of claim 34, wherein the modulator is an antagonist.

41. **(Canceled)** A method for screening for a therapeutic for treating or preventing a disease or condition that is associated with an IL-1 polymorphism comprising a proinflammatory haplotype comprising the steps of:

a) combining an IL-1 polypeptide or bioactive fragment thereof, an IL-1 binding partner and a test compound under conditions wherein, but for the test compound, the IL-1 protein and IL-1 binding partner are able to interact; and

b) detecting the extent to which, in the presence of the test compound, an IL-1 protein/IL-1 binding partner complex is formed, wherein an increase in the amount of complex formed by an agonist in the presence of the compound relative to in the absence of the compound or a decrease in the amount of complex formed by an antagonist in the presence of the compound relative to in the absence of the compound indicates that the compound is an effective therapeutic for treating or preventing the disease or condition.

42. **(Canceled)** A method of claim 41, wherein the agonist or antagonist is selected from the group consisting of: a protein, peptide, peptidomimetic, small molecule or nucleic acid.

43. **(Canceled)** A method of claim 42, wherein the nucleic acid is selected from the group consisting of: an antisense, ribozyme and triplex nucleic acid.

44. **(Canceled)** A method of claim 41, which additionally comprises the step of preparing a pharmaceutical composition from the compound.

45. **(Canceled)** A method of claim 41, wherein the IL-1 polypeptide is IL-1α.

46. **(Canceled)** A method of claim 41, wherein the IL-1 polypeptide is IL-1β.

47. **(Canceled)** A method of claim 41, wherein the IL-1 polypeptide is IL-1Ra.

48. **(Canceled)** A method for identifying a therapeutic for treating or preventing a disease or condition that is associated with an IL-1 polymorphism that comprises an inflammatory haplotype, comprising the steps of:

a) contacting an appropriate amount of a candidate compound with a cell or cellular extract, which expresses an IL-1 gene; and

b) determining the resulting protein bioactivity, wherein a decrease of an agonist bioactivity or a decrease in an antagonist bioactivity in the presence of the compound as compared to the bioactivity in the absence of the compound indicates that the candidate is an effective therapeutic.

49. **(Canceled)** A method of claim 48, wherein the modulator is an antagonist of an IL-1α or an IL-1β, bioactivity.

50. **(Canceled)** A method of claim 48, wherein the modulator is an agonist of an IL-1RN bioactivity.

51. **(Canceled)** A method of claim 48, wherein in step (b), the protein bioactivity is determined by determining the expression level of an IL-1 gene.

52. **(Canceled)** A method of claim 51, wherein the expression level is determined by detecting the amount of mRNA transcribed from an IL-1 gene.

53. **(Canceled)** A method of claim 51, wherein the expression level is determined by detecting the amount of the IL-1 product produced.

54. **(Canceled)** A method of claim 51, wherein the expression level is determined using an anti- IL-1 antibody in an immunodetection assay.

55. **(Canceled)** A method of claim 51, which additionally comprises the step of preparing a pharmaceutical composition from the compound.

56. **(Canceled)** A method of claim 51, wherein said cell is contained in an animal.

57. **(Canceled)** A method of claim 56, wherein the animal is transgenic.